

"deconditioning" in terms of cardiac responses to exercise in our patients, and phosphorus spectroscopy of muscle in the syndrome has shown no consistent disturbance of muscle energy metabolism.<sup>5</sup> The phenomenon may be of significance in the pathogenesis of "fatigue" in some patients, and it may be premature to conclude that neuromuscular function in all patients is normal, or that the "fatigue" is exclusively "central" in origin. Indeed, it may be presumptuous to consider chronic fatigue syndrome as a unitary entity.

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#### PET assessment of brain metabolic recovery in aphasia

The paper by Cappa *et al*<sup>1</sup> deals with the important issue of the mechanisms of recovery from aphasia. The authors longitudinally assessed two patients both neuropsychologically and by <sup>18</sup>F-2-fluoro-2-deoxy-D-glucose (<sup>18</sup>F-FDG) PET measurements of the local cerebral metabolic rate of glucose (LCMRGI). Each patient was studied twice with a three month interval. The LCMRGI values (19 brain regions on each side) were assessed for significant abnormalities at each study by comparison with values from a group of seven healthy subjects, while changes in LCMRGI from first to second PET study were assessed in each patient individually by an analysis of variance with one between-factor (acute and chronic stage) and one within-factor (left and right hemisphere). The authors conclude that (1) significant reductions in the LCMRGI of many brain regions were present in both patients at initial evaluation, and in one patient at second evaluation only; and (2) there was a significant increase in LCMRGI from first to second evaluation in each of the two patients.

We wonder whether the statistical procedures used were appropriate. Firstly, regarding the comparison with the control group, Cappa *et al* used two standard deviations below control mean as the cut-off for  $p < 0.05$ ; however, since the control group consisted of only seven subjects, the two-tailed  $t$  value for six degrees of freedom, or 2.447, should have been used instead. As this value is substantially larger than 2.0, it is likely that several of the LCMRGI values listed in tables 1 and 2 as statistically significantly reduced were, in fact, not. In addition,

the authors do not acknowledge the fact that there is a multiple testing problem as they are simultaneously assessing the atypicality of all regions.

Secondly, the analysis of variance procedure used to assess changes in LCMRGI from one study to the next in each subject is of serious concern. Apparently, it was run on the set of  $38 \times 2$  data (19 regions for each side of brain, two determinations), and yielded inordinately low probability levels (down to  $< 0.0001$ ) for single subject studies. Their way of using the analysis of variance in this and another study<sup>2</sup> would appear inadequate and possibly misleading. The authors do not point out the fact that region must also be a within-subject factor. In the case of measurements of LCMRGI, there exists a global scaling factor (the mean brain CMRGI), itself influenced by both physiological and methodological factors, that affects all regional values of a given subject. Thus, in the comparison of the two sets of LCMRGI data obtained in a single subject at two sequential studies, any change in this global factor will be repeated over all brain regions such that the more regions analysed, the larger the degrees of freedom and, in turn, the more statistically significant the findings. One way of turning around this problem would have been to covary for this global factor by, for example, an analysis of covariance.

When studying the changes in brain metabolism in a longitudinal fashion, more appropriate ways of testing whether a significant change in LCMRGI has occurred from one investigation to the next would be to assess each brain area either across a sufficiently large group of patients or, in single subjects, by checking the numerical changes observed against confidence limits established for the same region in a set of control subjects studied twice at similar time intervals (that is, confidence limits for reproducibility). The results presented by Cappa *et al* regarding recovery of LCMRGI must therefore be taken as descriptive only, pending confirmation from a better designed investigation.

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- 1 Cappa SF, Perani D, Bressi S, Paulesu E, Franceschi M, Fazio F. Crossed aphasia: a PET follow up study of two cases. *J Neurol Neurosurg Psychiatry* 1993;56:665-71.
- 2 Perani D, Vallar G, Paulesu E, *et al*. Left and right hemisphere contribution to recovery from neglect after right hemisphere damage. A <sup>18</sup>F-FDG PET study of two cases. *Neuropsychologia* 1993;31:115-25.

#### Cappa *et al* reply:

Drs Baron and Ford express their concern about the appropriateness of the statistical methods used to support the two major findings of our paper, namely that (1) a significant reduction of local cerebral metabolic rate for glucose was present in several regions, not only of the right, but also of the left hemisphere in two patients with crossed aphasia in the acute stage; and (2) a significant increase of metabolism occurred between the first and the second examination, three months after onset, in the same two patients.

Baron and Ford consider a cut off value equal to the mean minus two standard deviations

of LCMRGI of normal controls as inadequate, and suggest the use of the two-tailed  $t$  value for six degrees of freedom (2.447 SD). We think that the choice of a two-tailed value is questionable, as pathological values can *a priori* be expected to lie at the lower tail of the distribution (in the latter case, the cut off can be calculated as 1.943 SD—that is, approximately the same value used in our paper). Nevertheless, we have re-analysed our data using this ultra-conservative approach. Even adopting this criterion, the main finding of bihemispheric metabolic reduction was unchanged, and the regional results were only marginally different (case 1—examination I: no change; examination II: right 04 and 05 and left T3, T8, and T9 above the cut off; case 2—examination I: right and left T3, T4, T8, and T9 above the cut off). On the other hand, it is noteworthy that the latter values also fall below the fifth centile of the distribution of normal values from a larger sample of normal controls, which has been collected in our laboratory after the completion of this study.

Baron and Ford suggest that region should have been included as a within-subject factor in the analysis of variance. This design would, of course, be the most informative in the study of the regional correlates of functional recovery. Given the characteristics of our sample, however (two cases, with a very low probability to increase sample size within a reasonable time span), we had to forsake the important issue of regional effects and limit ourselves to the assessment of changes in hemispheric metabolism between the baseline evaluation and the follow up study in a  $2 \times 2$  factorial design. We think that any effort to remove "global" effects on the hemispheric values in this context would be questionable, given that the mean global cerebral metabolic rate is necessarily affected by intrahemispheric and transhemispheric diaschisis, namely, by the phenomenon under scrutiny.

Having said that, we appreciate that the description of two single cases is, by definition, "descriptive". Given the limited current understanding of crossed aphasia and of other instances of atypical cerebral dominance, to ascribe further explanatory power to our observations would be far fetched. The methodological suggestions by Baron and Ford, however, are rather impractical. To collect a "sufficiently large number of patients", given the incidence of crossed aphasia, would require a dedicated multicentre study. For radioprotection reasons, in some countries it would be difficult to perform two repeated studies with <sup>18</sup>F-FDG in normal subjects within three months.

We have proposed that patients with crossed aphasia may be particularly liable to distant effects, due to their bilateral language representation. Larger studies of the clinical correlations of distant effects and of their relationships with lesion characteristics, as well as with patient related variables (such as age, gender, handedness) are warranted to prove or disprove this specific hypothesis.

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